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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,647	KELLEY ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5 and 7-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5 and 7-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 16 September 2008 has been entered in full. Claims 23, 26, 31, 33 are amended. Claims 3, 6, and 34-38 are cancelled.

Election/Restrictions

Applicant's election of Group II, claims 1, 2, 4, 5, and 7-33 in the reply filed on 16 September 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1, 2, 4, 5, and 7-33 are under consideration in the instant application.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-2, 4-5, 7-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. Claims 1-2, 4-5, 7-33 are indefinite because they recite "Figure 1", "Table II", "Table III" and "Table VII". The claims are reading limitations from the specification into the claims. MPEP § 2173.05 states that "[w]here possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table 'is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claims.

Incorporation by reference is a necessity doctrine, not for applicant's convenience.' *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993)."

3. Claims 1, 8, 16, and 23-33 are indefinite because the elements recited in claims 1, 8 and 16 do not constitute proper Markush groups. First, regarding claims 8 and 16, the claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. Second, regarding claim 1, lines 5-6, the listing of amino acid substitutions does not use an "and" or an "or". See MPEP § 2173.05(h).

4. Claims 1, 9, 14, and 21-33 are indefinite because claims 1, 9, 14, 21, and 22 refer to "amino acid substitutions at the residue positions in Figure 1" or "DR5 receptor comprises amino acids 1 to 184 of Fig. 3A". Figures are not polypeptide sequences, but rather, contain polypeptide sequences. (Please note that this issue could be overcome by amending the claims to recite, for example "amino acid substitutions at the residue positions of the Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1)…" , "amino acids 1 to 184 of the polypeptide of SEQ ID NO: 4" or "amino acids 1 to 184 of the Apo-2 ligand polypeptide sequence of Fig. 3A".

Double Patenting

Statutory double patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The

filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Claims 1-2, 4-5, 7-33 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-2, 4-5, and 7-33 of copending Application No. 11/541,821. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Nonstatutory obviousness-type double patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1, 23-25, and 31-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-10, 12-13, 19-22, 24-39, 42-48, 58-67, and 81-82 of copending Application No. 11/541,828. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of

claims are drawn to an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more of the following amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO:1): S96C; S101C; S111C; R170C; K179C. Claim 23 of the instant application and claims 7-8, 19-20, 24-26, 30-32, 42-44 of the '828 application recite that the polypeptide is conjugated or linked to one or more polyols. Claims 24-25 of the instant application and claims 9-10, 21-22, 27-29, 33-35, 45-47 of the '828 application recite that the polyol is polyethylene glycol. Claims 31-32 of the instant application are directed to a composition comprising the Apo-2 ligand variant while claims 24-35, 63-67 of the '828 application are directed to a composition or pharmaceutical composition comprising the Apo-2 ligand variant. . Thus, the instant claims are not patentably distinct over the co-pending claims in Application No. 11/541,828.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 1, 23-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-10, 12-22, 24-39, 42-48, 58-70, and 81-82 of copending Application No. 12/283,351. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more of the following amino acid substitutions at the residue position(s) in Figure 1

(SEQ ID NO:1): S96C; S101C; S111C; R170C; K179C. Claim 23 of the instant application and claims 7-8, 19-20, 24-26, 30-32, 42-44 of the '351 application recite that the polypeptide is conjugated or linked to one or more polyols. Claims 24-25 of the instant application and claims 9-10, 21-22, 27-29, 33-35, 45-47 of the '351 application recite that the polyol is polyethylene glycol. Claims 26-30 of the instant application and claims 14-18 of the '351 application recite a nucleic acid molecule encoding the Apo-2 ligand variant, a vector, host cell, and method of making the Apo-2 ligand variant polypeptide. Claims 31-32 of the instant application are directed to a composition comprising the Apo-2 ligand variant while claims 24-35, 63-67 of the '351 application are directed to a composition or pharmaceutical composition comprising the Apo-2 ligand variant. Claim 33 of the instant application and claims 68-70 of the '351 application are drawn to a method of inducing apoptosis in mammalian cell comprising exposing expressing a DR5 receptor to the Apo-2 ligand variant polypeptide. Thus, the instant claims are not patentably distinct over the co-pending claims in Application No. 12/283,351.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 9, 22-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more of the following amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO:1): S96C; S101C; S111C; R170C; K179C. Claim 9 recites an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO: 1) and has a set of amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO: 1) selected from the group consisting of: Y189A:R191K:Q193K, Y189A:R191K:Q193K: H264R, Y189Q:R191K:Q193R: H264R:I266L:D267Q, Y189A:R191K:Q193K: H264D: I266L:D267Q: D269E, and Y189A:R191K:Q193R:H264S:I266L:D269E. Claim 22 recites an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO: 1) and has a set of amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO: 1) selected from the group consisting of:Y189Q:R191K:Q193R; H264R; I266L; D267Q ; Y189Q:R191K:Q193R; and Y189Q:R191K:Q193R:I266L. Claim 28 recites a host cell comprising a vector.

The specification of the instant application teaches that Apo-2 ligand variant polypeptides with specific amino acid substitutions are generated and the apoptotic activity of the native and pegylated variants is measured (pages 65-67, Example 8; page 69, Example 11; Figure 9). The specification also discloses that PEG-R170C-Apo2L and PEG-K179C-Apo2L variants are

cleared more slowly in the mouse than Apo2L.0 (page 69, Example 12). The phrase "an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) **and** has one or more of the following amino acid substitutions" (recited in claims 1, 9, 22; emphasis added by Examiner) has been interpreted by the Examiner as reading upon Apo-2 ligand variant polypeptides of SEQ ID NO: 1 with any number of deletions, substitutions, or additions *in conjunction with* one or more specific amino acid substitutions at positions 96, 101, 111, 170, 179, 189, 191, 193, 264, 266, 267, and 269. The claims of the instant application do not require that the polypeptide variants possess any particular conserved structure or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides and nucleic acids encoding such. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include actual reduction to practice, disclosure of drawings or structure chemical formulas, sufficient relevant identifying characteristics (such as, complete or partial structure, physical and/or chemical properties, and functional characteristics when coupled with a known or disclosed structure/function correlation), methods of making the claimed product, level of skill and knowledge in the art, predictability in the art, or any combination thereof. However, in this case, the specification fails to disclose and there is no art-recognized correlation between the structure of the genus of claimed polypeptides (and nucleic acids) and their function. The specification does not teach which amino acids can vary from SEQ ID NO: 1 and still result in a protein that retains activity. Therefore, the description of a few Apo-2 ligand variant polypeptides with specific amino acid substitutions and nucleic acids

encoding such is not adequate written description of an entire genus of functionally equivalent polypeptides and nucleic acids.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

Thus, the skilled artisan cannot envision the detailed chemical structure of the polypeptide and nucleic acid variants of the encompassed claims, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptides and nucleic acid molecules are required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated Apo-2 ligand variant polypeptide comprising one or more *specific* amino acid substitutions in the native Apo-2 ligand polypeptide amino acid sequence of SEQ ID NO: 1 (and a nucleic acid molecule encoding such), but not the full breadth of the

claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. Claims 1-2, 4-5, and 7-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated Apo-2 ligand variant polypeptide comprising one or more amino acid substitutions in the native Apo-2 ligand polypeptide amino acid sequence of SEQ ID NO: 1, wherein said one or more amino acid substitutions is selected from the group consisting of S96C, S101C, S111C, R170C, K179C, and H264C (and a nucleic acid molecule encoding such) *does not reasonably provide enablement for* an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more amino acid substitutions. The specification is not enabling for Apo-2 ligand variant polypeptides that comprises one or more amino acid substitutions at positions 189, 191, 193, 199, 201, 266, 267, and 269 of the native Apo-2 ligand sequence. Furthermore, the specification, while enabling for an isolated host cell, *does not reasonably provide enablement* for a host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is directed to an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more of the following amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO:1): S96C; S101C; S111C; R170C; K179C. Claim 2

recites that the Apo-2 ligand variant polypeptide comprises one or more amino acid substitutions recited Table II. Claim 7 recites that the Apo-2 ligand polypeptide comprises one or more amino acid substitutions at positions 189, 193, 199, or 201 of the native Apo-2 ligand sequence. Claim 9 recites an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO: 1) and has a set of amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO: 1) selected from the group consisting of: Y189A:R191K:Q193K, Y189A:R191K:Q193K: H264R, Y189Q:R191K:Q193R: H264R:I266L:D267Q, Y189A:R191K:Q193K: H264D: I266L:D267Q: D269E, and Y189A:R191K:Q193R:H264S:I266L:D269E. Claim 10 recites that the Apo-2 ligand variant polypeptide comprises one or more amino acid substitutions recited Table III. Claim 17 recites that the Apo-2 ligand variant polypeptide comprises one or more amino acid substitutions recited Table VII. Claim 22 recites an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO: 1) and has a set of amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO: 1) selected from the group consisting of:Y189Q:R191K:Q193R; H264R; I266L; D267Q ; Y189Q:R191K:Q193R; and Y189Q:R191K:Q193R:I266L. Claim 28 recites a host cell comprising a vector.

(i) The specification of the instant application teaches that Apo-2 ligand variant polypeptides with specific amino acid substitutions are generated and the apoptotic activity of the native and pegylated variants is measured (pages 65-67, Example 8; page 69, Example 11; Figure 9). The specification also discloses that PEG-R170C-Apo2L and PEG-K179C-Apo2L variants are cleared more slowly in the mouse than Apo2L.0 (page 69, Example 12). Example 13 of the

specification discloses that PEG-R170C-Apo2L.0 and PEG-K179C-Apo2L.0 caused a greater reduction in human COLO205 tumor volume than the same dose of Apo2L in a mouse xenograft model (bottom of page 69 through page 70). However, the specification does not teach that Apo-2 ligand variant polypeptides with amino acid substitutions at positions 189, 191, 193, 199, 201, 266, 267, 269 of the native Apo-2 sequence of SEQ ID NO: 1 have any function. Additionally, the phrase "an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) **and** has one or more of the following amino acid substitutions" (recited in claims 1, 9, 22; emphasis added by Examiner) has been interpreted by the Examiner as reading upon Apo-2 ligand variant polypeptides of SEQ ID NO: 1 with any number of deletions, substitutions, or additions *in conjunction with* one or more specific amino acid substitutions at positions 96, 101, 111, 170, 179, 189, 191, 193, 199, 201, 264, 266, 267, and 269. The specification does not teach any variant, fragment, or derivative of the Apo-2 ligand polypeptide other than the full-length amino acid sequences of SEQ ID NO: 1 with one or more amino acid substitutions selected from the group consisting of S96C, S101C, S111C, R170C, K179C, and H264C. The specification also does not teach any methods or working examples to demonstrate the functional characteristics of all the Apo-2 ligand polypeptide variants, fragments, and derivatives recited in the claims. Undue experimentation would be required by the skilled artisan to determine such.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid

substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

The assumption that Apo-2 ligand variant polypeptides with amino acid substitutions at positions 189, 191, 193, 199, 201, 266, 267, 269 of the native Apo-2 sequence of SEQ ID NO: 1

have any function or that Apo-2 ligand variant polypeptides of SEQ ID NO: 1 with any number of deletions, substitutions, or additions *in conjunction with* one or more specific amino acid substitutions at positions 96, 101, 111, 170, 179, 189, 191, 193, 199, 201, 264, 266, 267, and 269 have a biological activity cannot be accepted in the absence of supporting evidence because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Wuyts et al. (J Immunol 163: 6155-6163, 1999) establish that NH_2-and COOH- terminal truncations of granulocyte chemotactic protein-2 (GCP-2) have enhanced neutrophil chemotactic potency as compared to wild-type GCP-2 (abstract; pg 6157-6158). Sher et al. (J Biol Chem 274(49):35016-35022, 1999) disclose that keratinocyte growth factor (FGF-7) acts predominantly on cells of epithelial origin and regulates processes in embryonal and adult development, including cell growth, differentiation, cell migration, and repair of epithelial tissues (pg 35016, ¶ 1). Sher et al. demonstrate that point mutations in a loop of FGF-7 do not alter receptor binding affinity, but cause reduced mitogenic potency and reduced ability to induce receptor-mediated phosphorylation events (pg 35020-35021). Additionally, a SCF mutant called Steel^{17H} (Sl^{17H}) induces melanocyte defects and sterility in males. The Sl^{17H} allele contains a mutation that results in the substitution of 36 amino acids in the SCF cytoplasmic domain with 28 novel amino acids (Kapur et al., Blood 94(6): 1915-1925, 1999). Kapur et al. teach that compound heterozygous Sl/Sl^{17H} mice manifest several hematopoietic abnormalities in vivo, such as red blood cell deficiency, bone marrow hyperplasia, and defective thymopoiesis (pg 1917-1918; Figures 2-3). In vitro, both the soluble and membrane-associated Sl^{17H} isoforms exhibit reduced cell surface expression on stromal cells and diminished biological activity as

compared to wild soluble and membrane-associated forms (abstract, pg 1919-1921; Figures 6-7). Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Finally, Hymowitz et al. teach that the Apo-2 ligand structure represents the first example of metal binding-mediated trimerization of a cytokine, wherein alanine or serine substitutions of Cys230 or removal of the bound zinc metal indicate the zinc binding site is essential for full bioactivity (Biochemistry 39:633-640, 2000; page 635, column 2, 3rd full paragraph; page 637, column 1, last paragraph). Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, the specification fails to teach the skilled artisan how to make and use biologically active Apo-2 ligand variant polypeptides without resorting to undue experimentation to determine what the specific biological activities of the variants are.

(ii) The Examiner has interpreted claim 28 as reading on an isolated host cell, as well as a host cell in the context of a multicellular, transgenic organism and a host cell intended for gene therapy. The specification of the instant application teaches that suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells (page 37, lines 33-34). At page 38, lines 7-9, the specification teaches that suitable host cells for the expression of glycosylated Apo-2 ligand are derived from multicellular organisms. The specification also states that transformation means introducing the DNA into an organism so that the DNA is replicable (page 38, lines 22-23) and can be done using standard techniques, such as calcium treatment, ultrasound, calcium phosphate precipitation, nuclear microinjection,

electroporation, bacterial protoplast fusion (page 38, lines 24-40 through page 39, lines 1-8). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with an incorporated Apo-2 ligand variant nucleic acid molecule is demonstrated to express the Apo-2 ligand variant polypeptide. There are also no methods or working examples in the specification indicating that a multicellular animal has an Apo-2 ligand variant "knocked in". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses that one possible technique used to introduce an Apo-2 ligand variant nucleic acid into a mammalian cell includes nuclear microinjection. However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even rarer than random events. Therefore, in view of the extremely low frequency of both

targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention.

Furthermore, the instant specification does not teach any methods or working examples that indicate an Apo-2 ligand variant nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the Apo-2 ligand variant nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express an Apo-2 ligand variant nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express an Apo-2 ligand nucleic acid in the cell of an organism or be able to produce an Apo-2 ligand variant polypeptide in that

cell. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell…").

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, to generate a transgenic animal expressing an Apo-2 ligand variant polypeptide, and to introduce and express an Apo-2 ligand variant nucleic acid in a cell of an organism for therapy; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity and how to introduce an Apo-2 ligand variant nucleic acid in the cell of an organism to be able produce that Apo-2 ligand variant; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 2, 4-5, 8, 10, 12-13, 16, 17, 19-20, 26-31, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Hymowitz et al. (Biochemistry 39: 633-640, 2000).

Hymowitz et al. teach Apo-2 ligand variant polypeptides comprising amino acid substitutions at positions 201, 264, or 269 in the native Apo-2 ligand polypeptide amino acid sequence of SEQ ID NO: 1 (and nucleic acid molecules encoding such) (page 637, Table I). Specifically, Hymowitz et al. teach mutants K201A, H264A, and D269A, which are disclosed in Tables II, III, and VII of the instant application (as recited by claims 2, 10, and 17). Hymowitz et al. teach that the mutants are constructed by oligonucleotide-directed mutagenesis of a plasmid and that *E. coli* strain 294 is transformed with the mutated plasmids (page 634, column 1, first full paragraph). Hymowitz et al. disclose that the mutants are expressed and purified (page 634, column 1, first full paragraph). The bioactivity of the Apo-2 ligand mutants is determined by measuring the cell viability of SK-MES-1 human lung carcinoma cells in the presence of the mutants (page 634, column 2, 2nd full paragraph; Table 1, page 637).

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Ashkenazi et al. U.S. Patent 6,470,739 (substitutional variants of Apo-2 ligand; in particular, disclose an Apo-2 ligand polypeptide fragment in conjunction with a substitution at position 269; same assignee and one common inventor)

Kelley et al. (US 2004/0186051; Apo-2 ligand variant polypeptides with amino acid substitutions; same assignee and 2 common inventors; case abandoned)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
02 January 2009

/Bridget E Bunner/
Primary Examiner, Art Unit 1647